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10/594,233	09/25/2006	Stephen Robert Wedge	056291-5303	3400

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EXAMINER	
FRAZIER, BARBARA S	
ART UNIT	PAPER NUMBER
1611	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,233	WEDGE, STEPHEN ROBERT	
	Examiner	Art Unit	
	BARBARA FRAZIER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/28/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 15-17are pending in this application.

2. Cancellation of claims 21 and 24 is acknowledged. Claims 1-14, 18-20, 22, and 23 already stand canceled.

3. Claims 15-17 are examined.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. The provisional rejection of claims 15-17, 21, and 24 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 4,

and 15 of copending application No. 10/563,439 in view of Hennequin et al (WO 00/47212) is withdrawn in view of the fact that 10/563,439 is now abandoned.

6. Claims 15-17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12-18 of copending Application No. 10/594,234, or alternatively over claims 21-24, 27, 28, and 31-34 of 10/594,235; claims 11, 12, and 15-24 of 11/994,824; claims 11-17 of 12/158,266; or claims 13-21 of 12/408,833 in view of Hennequin et al (WO 00/47212).

The claimed invention is drawn to method for the treatment of a solid tumor cancer in a warm-blooded animal in need thereof, which comprises administering to said animal an effective amount of AZD2171, or a pharmaceutically acceptable salt thereof, before, after, or simultaneously with an effective amount of one of 5-FU, CPT-11, or 5-FU and CPT-11 (see claim 1).

Copending application 10/594,234 (or alternatively the claims of 10/594,235; 11/994,824; 12/158,266; or 12/408,833) claims a method for the treatment of a cancer in a warm-blooded animal in need thereof which comprises administering to said mammal an effective amount of AZD2171 with another therapeutic agent, optionally with an effective amount of ionizing radiation.

The copending applications do not claim the administration of CPT-11 and/or 5-FU with the AZD2171.

Hennequin et al teach administration of quinazoline derivatives as angiogenesis inhibitors, such as solid tumors (abstract and page 83), and exemplify AZD2171

(Example 240). Hennequin et al further teach that, in the field of medical oncology, it is normal practice to use a combination of different forms of treatment to treat each patient with cancer, including radiotherapy and chemotherapy; antiproliferative/antineoplastic drugs and combinations thereof which may be used include 5-fluorouracil (5-FU) and irinotecan (CPT-11) (see pages 85 and 86).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to administer 5-fluorouracil and/or irinotecan with AZD2171 of the copending applications; thus arriving at the claimed invention. One skilled in the art would be motivated to do so because Hennequin et al fairly teach and suggest the use of said compounds in conjoint treatment with quinazoline derivatives such as AZD2171.

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

7. Applicant's arguments filed 4/28/10 have been fully considered but they are not persuasive.

Applicant argues that, while Applicant does not agree with the Examiner's argument of obviousness-type double patenting, Applicant need not, and in fact cannot respond to this ground for rejection unless and until claims are allowed in one or more of the reference applications before allowance of the present application. Since Applicant has not responded to any points of rejection, the provisional rejections stand for reasons stated above.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hennequin et al (WO 00/47212).

The claimed invention is drawn to method for the treatment of colorectal cancer in a warm-blooded animal in need thereof, which comprises administering to said animal an effective amount of AZD2171, or a pharmaceutically acceptable salt thereof, before, after, or simultaneously with an effective amount of one of 5-FU and CPT-11 (see claim 1).

Hennequin et al teach administration of quinazoline derivatives as angiogenesis inhibitors, such as solid tumors (abstract and pages 83 and 86), and exemplify AZD2171 (Example 240). Hennequin et al teach that AZD2171 is one of thirteen "more especially preferred compounds" (page 58, lines 24-28), thus motivating its selection from the quinazoline derivatives of Formula I disclosed in the reference. Hennequin et al further teach that, in the field of medical oncology, it is normal practice to use a combination of different forms of treatment to treat each patient with cancer, including radiotherapy and chemotherapy; antiproliferative/antineoplastic drugs and combinations thereof which may be used include 5-fluorouracil (5-FU) and irinotecan (CPT-11) (see pages 85 and 86), compounds known to one skilled in the art to be suitable for the

treatment of colorectal cancer. Hennequin et al teach that the compounds may be used to treat solid tumors of, for example, the **colon**, breast, prostate, lungs and skin (page 86).

Hennequin et al do not specifically teach the combination of AZD2171 with 5-floruouracil and/or irinotecan.

However, it would have been obvious to a person having ordinary skill in the art at the time the invention was made to administer 5-fluorouracil and/or irinotecan with AZD2171; thus arriving at the claimed invention. One skilled in the art would be motivated to do so because Hennequin et al fairly teach and suggest the administration of antiproliferative/antineoplastic drugs and combinations thereof including 5-fluorouracil (5-FU) and irinotecan (CPT-11), such that it would be within the purview of the skilled artisan to select said compounds for administration by routine experimentation, in order to optimize the efficacy of the resultant composition.

Regarding claim 16, Hennequin et al teach that radiotherapy may be used in conjoint treatment with the selected chemotherapy (page 85).

Regarding claim 17, Hennequin et al teach the compound AZD2171 formed as its free base (Example 240).

Response to Arguments

10. Applicant's arguments filed 4/28/10 have been fully considered but they are not persuasive.

Regarding the *prima facie* case of obviousness, Applicant argues that there is nothing in the disclosure of Hennequin, when considered as a whole, that would suggest or otherwise lead the skilled person to specifically select 5-FU or CPT-11 out of the "enormous listing" of generic and "for example" possibilities and then specifically select, out of the broad generic teachings and hundreds of examples of Hennequin compound, to combine it with the compound of Example 240, AZD2171, and then administer the combination specifically for the treatment of colorectal cancer as presently claimed.

This argument is not persuasive. With regard to the instantly claimed AZD2171, this compound is explicitly disclosed in Example 240 (page 251, line 21 to page 252, line 10) and is taught by Hennequin et al to be a "more especially preferred" compound of the invention (page 58, lines 24-28). Thus, while Hennequin et al broadly disclose a genus of compounds, AZD2171 is one of thirteen "more especially preferred compounds", thus motivating its selection from the quinazoline derivatives of Formula I as broadly disclosed in the reference. With regard to treating colorectal cancer, Hennequin et al teach that the compounds disclosed therein inhibit the effects of VEGF, a property of value in the treatment of disease states associated with angiogenesis and/or increased vascular permeability such as cancer (page 2, lines 15-17; page 84, lines 6-13 and 18-22; and page 85, lines 11-23), including cancer of the colon as recited in claims 15-17 (page 86, line 23). With regard to combination therapy, Hennequin et al teach that it is **normal practice** to use a combination of different forms of treatment to treat each patient with cancer (page 85, lines 2-3). Thus, there is nothing unobvious

about selecting two agents that are taught in the prior art to be useful for the treatment of cancer and combining them for use in the treatment of cancer. While Hennequin et al do teach several classes of compounds useful in this combination therapy, 57 compounds are specifically named as being known in the prior art for treating cancer and useful in combination with the quinazoline derivatives of its invention; 5-FU and CPT-11 are specifically named (pages 85 and 86). Selecting 5-FU or CPT-11 from a list of 57 named compounds falls within the realm of routine experimentation, that is, choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Regarding secondary considerations, Applicant argues that any *prima facie* case of obviousness is overcome by the comparative data presented in the specification at pages 34-39 and in Figures 1-4. Applicant argues that the Examiner's disregard of the 3 mg/kg AZD2171 data is improper because the dosage range of 0.03-1.5 mg/kg is the suggested human dosage, while the dosages in the data are those given to mice.

Applicant then asserts that "the Examiner has confused suggested human dosages in the specification with doses given to mice in animal testing, and has improperly extended the patenting role of the USPTO into the safety and efficacy role of the FDA." Applicant then provides a lengthy discussion that such a requirement is (1) directly contrary to the Federal Circuit decision in *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995), which expressly sanctions the use of statistically significant data from art accepted animal models for purposes of patentability (as opposed to requiring human clinical data); (2) is contrary to the Federal Circuit decision in *In re Chupp*, 2 USPQ2d 1437 (Fed. Cir. 1987) that to overcome *prima facie* obviousness one need only show that the claimed composition possessed superior activity in one embodiment, and (3) is contrary to the well established principle that a valid claim may encompass inoperative species or embodiments, and in any event (4) the specification discloses appropriate dose ranges and routes of administration for the components of the claimed composition in a manner sufficient to meet the enablement requirements of section 112.

These arguments have been considered, but are not persuasive. It is first noted that Applicant's arguments regarding consideration of the 3 mg/kg AZD2171 data is found to be persuasive, and therefore said data has been considered. However, this data, in combination with the 1.5 mg/kg AZD2171 data in the specification, is still not sufficient to overcome the rejection. Regarding Applicant's point (1), it is noted that the issue is not whether or not accepted animal models may be used for purposes of patentability, but whether or not said data is commensurate in scope with the claims, as discussed below. Regarding Applicant's points (2) and (3), it is noted that, even though

Applicant is not required to show unexpected results over the entire range of properties possessed by a chemical compound or composition, evidence presented for a narrower range is sufficient to rebut the *prima facie* case of obviousness for a broader range **if** a skilled artisan "could ascertain a trend in the exemplified data that would allow him to **reasonably** extend the probative value thereof." While the claims may encompass inoperative embodiments, the remaining (operative) data must still be sufficient to ascertain trend to reasonably extend its probative value to that which is commensurate in scope with the claims. Regarding Applicant's point (4), it is noted that the claims are not currently rejected under 35 U.S.C. 112, first paragraph, and thus these arguments are not applicable at this time.

For AZD2171 in combination with 5-FU, the data for 5-FU (50 mg/kg 1x weekly) in combination with AZD2171 at a concentration of 1.5 mg/kg/day, does not demonstrate significantly better results over AZD2171 alone, since the results up to day 25 appear to overlap statistically, and at day 25, there appears to be no improved effect from the combination of AZD2171 and 5-FU over the use of AZD2171 alone. Therefore, the only data which shows significantly better results for 5-FU is when AZD2171 is used at a concentration of 3 mg/kg/day. Since the data shows that results are not significantly improved at 1.5 mg/kg/day, the single concentration of 3 mg/kg/day is not sufficient to ascertain a trend to extend the probative value thereof to any effective amount of AZD2171. Regarding the phrase, "effective amount", Applicant's specification does teach that an example of an effective amount for a human (which is a warm-blooded animal as recited in the claims) is 0.03-1.5 mg/kg. While one skilled in

the art would recognize that adjustments in dosage concentrations would be made between animal models and human dosages, Applicant has not demonstrated that the single concentration of 3 mg/kg/day AZD2171 and 5FU in a mice animal model is sufficient to ascertain a trend to reasonably extend the probative value thereof to any effective amount of said compound in any warm-blooded animal, which includes 0.03-1.5 mg/kg/day in a human, as taught by Applicant's specification. Therefore, the data presented is not commensurate in scope with the claims.

For AZD2171 in combination with CPT-11, while Applicant's data shows improved results at AZD2171 concentrations of 1.5 mg/kg/day and 3 mg/kg/day, the full range of effective amounts of AZD2171 in a warm-blooded animal include amounts as little as 0.03 mg/kg/day, as taught by Applicant's specification. This amount is **50 times smaller** that what is tested in Applicant's data (Figures 1-4). While one skilled in the art would recognize that adjustments in concentration could be made between accepted animal models and human dosages, it is not clear that the concentrations of 1.5 mg/kg/day and 3 mg/kg/day are sufficient to ascertain a trend which would **reasonably** extend the probative value thereof to a concentration **50 times smaller** than what has been tested, with the same results. Therefore, the data presented is not commensurate in scope with the claims.

Therefore, it is the Examiner's position that the claims are rendered obvious.

Conclusion

No claims are allowed at this time.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BARBARA FRAZIER whose telephone number is (571)270-3496. The examiner can normally be reached on Monday-Thursday 9am-4pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BSF

/Ashwin Mehta/

Primary Examiner, Technology Center 1600